from oral lesions and clinical symptoms recorded. The median age of the 4 females and 2 males was 50.5 years. All patients had signs of OC with tongue plaques manifesting at a median of 86 days post-HCT (range 30-1045) and symptoms of dry mouth, anorexia, nausea and/or vomiting. Dysguesia was noted in three patients and weight loss in five (median 18 kg). None had odynophagia and EGD performed in 3 patients was negative for esophageal candidiasis. A total of 24 isolates were evaluated, with those tested being resistant to fluconazole, itraconazole, and voriconazole with respective MIC's of >256 μ/ml, 44 μ/ml and 14.7 μ/ml. All isolates were sensitive to amphotericin B (MIC 0.38 μ/ml). Concurrent systemic antifungal therapy at the time of diagnosis of OC comprised: fluconazole, voriconazole, caspofungin or micafungin, or combination regimens of caspofungin, micafungin, or amphotericin B lipid complex with voriconazole. The signs and symptoms persisted despite continuation or alterations in the systemic antifungal regimen. Topical application to the oral mucosa (5 ml 2-4 times/day) of amphotericin B oral suspension (ABOS), prepared by the pharmacy at a concentration of 100 mg/ml, resulted in dramatic clinical response with rapid resolution of symptoms in all 6 patients. OC relapsed at a median of 65.3 days in all the patients necessitating re-treatment with ABOS. All patients rapidly responded. We conclude that ABOS provides a simple, highly effective and low-cost option for treatment of *C. glabrata* OC. The use of newer antifungal agents combined with the incidence and morbidity of other non-*albicans* OC infections may provide future directions of study.

HCT Patient Characteristics

Age	Sex	Diagnosis	Transplant Characteristics	GI GvHD	Concurrent Antifungal Therapy
39	F	CML-BC	MRD, Cy/TBI (12 Gy)	Acute	FLUC, VORI
51	M	MM/PCL	MRD, Flu/Mel/Cam	Chronic	FLUC, VORI
47	F	T-ALL/AML	MMUD, Cy/TBI/ Cam (12 Gy)	N/A	FLUC
60	F	DLBCL/NHL	MUD, Flu/Mel/Cam	Acute	VORI, CASP, MICA
50	F	CML-BC	MMUD, Flu/TBI/ Cam/CD45 (4.5 Gy)	N/A	VORI, CASP, ABLC, MICA
58	M	MDS	MRD, Flu/TBI/Cam (4.5 Gy)	Chronic	FLUC, VORI, CASP, MICA

Abbreviations: CML-BC: Chronic Myelogenous Leukemia in Blast Crisis; MM/PCL: Multiple Myeloma/ Plasma Cell Leukemia; T-ALL/AML: T-cell Acute Lymphoblastic Leukemia/ Acute Myeloblastic Leukemia; DLBCL/NHL: Diffuse Large B-cell Lymphoma/Non Hodgkin's Lymphoma; MDS: Myelodysplastic Syndrome; MRD: Matched Related Donor; MMUD: Mis-matched Unrelated Donor; MUD: Matched Unrelated Donor; Cy: Cyclophosphamide; TBI: Total Body Irradiation; Flu: Fludarabine; Mel: Melphalan; Cam: Alemtuzumab; CD45: Investigational Anti-CD45 Monoclonal Antibody; FLUC: Fluconazole; VORI: Voriconazole; CASP: Caspofungin; MICA: Micafungin; ABLC: Amphotericin B Lipid Complex

428

PALONOSETRON FOR THE PREVENTION OF ACUTE AND DELAYED NAUSEA AND VOMITING FOLLOWING HIGH DOSE MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION

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Recipients of autologous stem cell transplanatation(HSCT) with high dose melphalan universally experience significant acute and delayed nausea and vomiting(N/V)(60-100%), with the number of emetic episodes typically increasing over advancing days. Currently no drugs with FDA approval for delayed N/V have been studied in recipients of HSCT. Palonosetron, a serotonin antagonist(5HT3) with a prolonged duration of action, is approved for acute and delayed onset N/V following moderate to highly emetogenic chemotherapy. A retrospecive study was undertaken to determine if the type of 5HT3 used, affected the amount of N/V experienced and the number of antiemetics used to treat breakthrough N/V. The treatment group included 25 myeloma patients who received 0.25mg palonsetron prior to HDM followed by HSCT. Melphalan dose(m2)= 200mg(n=22),140mg(n=2) 100mg(n=1). The control group was comprised of 49 patients who received 24mg IV ondansetron prior to HDM. The groups were otherwise comparable.There were no scheduled anti-emetic from day0 onwards, and anti-emetics were administered "as needed" based on patient needs as asssessed by nurse clinician or clinical rounds team. As needed meds includeed lorazepam , prochlorperazine, metoclopramide, promethazine, ondansetron alone or in combination. Evaluation of nausea and vomiting was assessed via interview with patient and review of input/output in medical chart.

Table 1 shows results of palonosetron versus ondansetron and the use of breakthrough medications. There was a statistically significant reduction in the number of breakthrough medications needed for both acute and delayed N/V with respect to any breakthough medications(days 1-4) or versus additional ondansetron only((all 7days). In addition , cost analysis revealed the following-(all quoted from Redbook 2006): Average daily cost of breakthrough medications for palonosetron and ondansetron group = $14.00 and $56.20 respectively. Average overall cost/patient(including prevention) for palonosetron = $477 versus ondansetron.=$511. There were no differences in time to engraftment or significnat side effects between groups.

We conclude that the use of palonosetron before HDM prior to autologous transplantation was more effective that ondansetron in controlling acute and delayed nausea and vomiting and improving quality of life. In addition, because of its long duration of action, palonosetron decreased the need for additional 5HT3 antagonists leading to overall cost savings.

Breakthrough nausea and vomiting

Day 0-HSCT	Nausea/ Vomiting (%)	any drug used for breakthrough: Palonosetron (n=25)	Ondansetron (n=49)	P-value	ondansetron used for breakthrough: Palonosetron (n=25)	Ondansetron (n=49)	P-value
0	7/3	30	84	<.001	0	41	<.001
1	48/26	48	78	<.024	4	51	<.001
2	60/7	66	86	<.05	11	59	<.05
3	48/10	48	92	<.001	15	59	<.05
4	55/18	66	90	<.04	11	47	<.01
5	37/7	70	84	ns	15	53	<.006
6	40/25	60	86	<.05	19	47	<.05

429

VORICONAZOLE PROPHYLAXIS IN PATIENTS AT HIGH RISK FOR INVASIVE FUNGAL INFECTIONS FOLLOWING ALLOGENEIC HEMATAPOETIC STEM CELL TRANSPLANTION

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Voriconazole is a triazole antifungal agent with good activity against *Aspergillus* spp. Standard antifungal prophylaxis at NMH for recipients of allogeniec HSCT is itraconazole 200mg po bid. Voriconazole 200mg po bid is substituted on day0 of transplant if they have prior history of Aspergillus infection(secondary prophylaxis) or switched from itraconazole to voriconazole with receipt of high dose steroids(methylprednisolone 2mg/kg) for GVHD. Voriconazole is discontinued 30 days after immunosuppression is stopped. 80 allograft recipients who received voriconazole and in whom complete microbiologic and pharmacokinetic data were available were studied to determine the efficacy of voriconazole in preventing invasive fungal infections (IFI). 24 patients had no itraconazole prophylaxis. The remainder (n=56) received itracon-

azole for 1-161 days (median 7). The length of voriconazole therapy was 6-956 days (median 120). The total number of patient-days on voriconazole was >14,000d. A total of 10 IFIs were seen in patients on voriconazole: *Candida glabrata* (n=5), *Candida krusei* (n=1), *Cunninghamella* (n=1), *Rhizopus* (n=2), and *Mucor* (n=1).Although 4 cases of zygomycosis were seen, no case of *Aspergillus* infection was seen. The actuarial probability of zygomycosis or any invasive fungal infection is 7% and 18% respectively.

Zygomycetes are not susceptible to voriconazole, and breakthrough infections are not surprising. In clinical trials *C. glabrata* and *C. krusei were* susceptible to voriconazole at MIC90=.5-2mcg and the majority of fluconazole resistant C.Glabrata isolates have MIC90s>1mcg.dose. Interestingly, steady-state trough voriconazole levels were <0.2, <0.2, 0.33, 0.55, 0.63, and 1.78 mcg/mL in the 6 candidiasis cases. C.Glabrata in patient with vori level=1.78 was fluconazole resistant(c/s not avaiable for other Candida specimens). All 6 candidiasis cases were seen amongst the 44 patients when voriconazole levels < 2 mcg and none amongst the 36 with levels of >2 mcg (P=0.061; Fishers exact test), consistent with a study correlating voriconazole levels and clinical success in aspergillosis (Smith et al. Antimicrob Agents Chemother 2006;50: 1570-1572).

Voriconazole is extremely effective in preventing aspergillus infections but Zygomycosis remains a concern in voriconazole-treated patients. Therapeutic drug monitoring with dose adjustment may be indicated in patients on voriconazole to avoid infections with fungi that are otherwise susceptible to the drug.

breakthrough infections

Organism	Site	Days of exposure to voriconazole	Days post transplant	Concommitant infection/neutropenia	GVHD	Number of days of prior exposure to itraconazole	Voriconazole level
C.Krusei	lung	157	183	E.coli and VRE/no	GI	26	0.53
C.Glabrata	lung	136	145	VRE/yes	GI	9	0.63
C.Glabrata	lung	832	837	MRSE/yes	GI/Skin	7	0.20
C.Glabrata	lung	159	179	MRSA and Enterobacter/yes	GI/Skin	20	1.78
C.Glabrata	lung	56	137	MRSA and Strept/yes	GI/Skin	122	0.33
C.Glabrata	lung	7	9	VRE/yes	GI/Skin	7	0.33
Rhizopus	sinus	128	135	VRE/no	Skin	7	4.1
Rhizopus	lung	7	55	none/no	none	128	5.9
Mucor	lung	77	77	E.coli/no	Skin	0	3.5
Cunninghamella	lung	17	90	CONS/yes	GI	64	1.1

430

DISCORDANCE BETWEEN VORICONAZOLE DOSE AND PLASMA CONCENTRATIONS: IMPLICATIONS FOR THERAPEUTIC BLOOD MONITORING

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There is limited data on the effects of drug levels on therapeutic success in fungal infections. A significant correlation between plasma voriconazole levels(>2) and successful Aspergillosis outcomes was reported.(Smith et al.Antimicob Agents Chemother 2006;(50):1570-2). Pharmacodynamic studies as well as recently proposed CSLI voriconazole breakpoints suggest a need for therapeutic monitoring. Multiple drugs used during HSCT can affect the liver cytochrome P450 system, which plays a significant role in voriconazole metabolism. Likewise, voriconazole also exhibits genetic polymorphism. Extensive metabolizers have a significantly lower exposure to voriconazole than poor metabolizers. In a small trial including 22 patients (Trifilio et.al.BMT 2005(5)509) wide interpatient variablilty in plasma voriconazole levels was reported for patients receiving equivalent doses of voriconazole, many with levels below the MIC(90) for Candida and Aspergillus.

In this study, steady-state plasma trough voriconazole levels were measured after at least 5 days of therapy in 94 patients after HSCT on 208 separate occassions (median=2;range=1-5). Most patients had undergone allogeneic HSCT. Plasma voriconazole levels were measured using standard HPLC method. The daily voriconazole dose was 200 mg (n=4), 400 mg (n=157), 500 mg (n=20), 600 mg (n=19), and 800 mg (n=8);corresponding to 2.0-16.3 mg/kg (median 5.4). The voriconazole levels were <0.2-12.5 mcg/mL (median 1.2). In keeping with the non-linear pharmacokinetic profile of the drug, a strong correlation was not seen between the dose and levels.

(P<.05)

The table below shows the relationships between levels and dose. While the amount of drug administered in mg//kg was significantly higher when levels were > 5mcg/ml, there was no consistent relationship between dose and level below that threshold (P value<0.05).

We conclude that adult patients receiving standard doses of voriconazole have highly variable drug levels. Over 37% of the voriconazole levels were below the suggested breakpoints for C.Glabrata and C.Krusei , and over 60% would be associated with a greater likelihood of failure for Aspergillus infection. Future voriconazole studies should include therapeutic drug monitoring, and until this is clarified, patients should be monitored especially for those with confirmed life-threatening infections.

Voriconazole levels and dose

Voriconazole dose/day(mg)	n	median voriconazole level (range)	average dose (mg/kg)	percent of levels <0.5mcg	percent of levels <1.0mcg	percent of levels < 2.0mcg
200	4	1.66 (0-3.07)	3.3	25	25	50
400	157	1.09 (0-11.1)	5.2	28	45	65
500	20	1.66 (0-5.99)	6.3	20	40	55
600	19	1.5 (0-6.75)	8.9	21	31	58
800	9	2.06 (0-12.5)	10.8	33	33	50